(51) International Patent Classification 5 : G06F 15/42	A1	(11) International Publication Number: WO 94/06088
		(43) International Publication Date: 17 March 1994 (17.03.94)

(54) Title: METHOD AND APPARATUS FOR CONTROLLED INDIVIDUALIZED MEDICATION

(57) Abstract

A method and a device for giving patients individualised, situation-dependent medication advice are disclosed. Preferably, the invention is implemented in portable computers. The method is founded on knowledge-based computer technology and comprises a reminder function (1), a recording and storage function (2, 3), as well as a function for inductive data analysis (4) and rule generation. When the knowledge-based system (6) finds that a medicine should be taken, the computer emits a signal providing information on the type of medicine and the dose. The patient records the intake of medicine as well as his current state of health. This information is stored in a database together with the point of time. Inductive data analysis is used to spot the relationship between various events and symptoms as well as establish medication rules. These rules are refined upon as new information is recorded in the database, and are automatically adapted to changes in the patient's state of health.

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Method and apparatus for controlled individualized
medication.

This invention relates to a method for controlled
individualised medication.

5   Many chronic diseases in man require the administra-
tion of various substances in order to counteract the dis-
ease and/or to keep down its symptoms. Medication often
includes several different pharmaceutical preparations,
each having its specific properties, duration of action,

10 and so forth. Dosage and time intervals between admini-
strations depend on the status of the disease, patient-
specific factors, such as inheritance, age, weight, gene-
ral state of health as well as diet and physical activi-
ties. As a result, medication is a fairly complicated

15 task to perform. In practice, this will manifest itself
as variations in the patient's state of health. In the
case of some diseases, such as Parkinson's disease, the
symptoms may in a single day vary from making the patient
incapacitated for work (rigidity, tremor, etc.) to leaving

20 the patient almost untroubled.

There are several different methods used for provid-
ing recommendations as to the dosage and the time inter-
vals between administrations. These recommendations are
often founded on the adjustment of an initial concept

25 based on pharmacokinetic information on the various pre-
parations. The adjustments are made on the basis of recor-
dations of the patient's condition on various occasions.
This information is interpreted by specialists, and used
for adjusting the dosage and the time intervals.

30   However, the methods currently used do not yield
desirable results, the reason being that the pharmacokine-
tic effects of the preparations are not absolutely clear.
The way the preparations move through the body is affected
by interactions with other preparations, enzymes and so

35 forth, during the absorption and the distribution phase
as well as during the metabolism and the secretion phase.
Thus, the actual concentration of a preparation in the

2

biophase, the duration of action and the effect cannot be
predicted statistically using monotonic models. Another
reason is that the evaluation of the patient's data is a
complex operation since it involves many dependent vari-
5   ables and since it further is difficult to lay down analy-
tical models.

It is likely that the state of health of certain
groups of patients can be drastically improved by optimum,
individualised and situation-dependent medication. This
10 would result in enhanced quality of life, as well as fewer
sickness pensioners.

GB 2,218,831 teaches an apparatus for helping people
suffering from chronic diseases, such as diabetes, to
determine medication doses and keep a suitable diet,
15 thereby to improve their state of health. This apparatus
has a key pad for entering data on the blood glucose
levels as well as the physical activity of the patient,
a memory where e.g. data on the prescribed dosage are
stored, a program for computing suitable doses of insulin
20 on the basis of inputted data as well as data stored in
the memory, and a display for showing the doses of insulin
computed.

Similar apparatus are described in US Patent
5,019,974 and EP Patent Application 0 128 054.
25   These prior-art apparatus are all based on there
being a known relationship between a condition of the
patient, such as the blood glucose level, and the well-
being of the patient, and on the medication having a known
effect on the patient. Thus, one may establish fixed medi-
30 cation rules valid for comparatively long periods of time.

However, in the case of other chronical diseases,
such as Parkinson's disease, epilepsy and abnormal blood
pressures, there does not exist any single actual value or
condition of the patient that can be measured and corre-
35 lated with the well-being of the patient. For these dis-
eases, medication generally includes several medicines,
whose precise interactions and effects on the patient are

3

not fully known. In addition, the health condition of the
patient is affected by a plurality of external factors.
Thus, it is impossible to establish fixed medication rules
valid for long periods of time, and the prior-art appara-
5   tus therefore cannot be used for controlled individualised
medication in the treatment of more complicated diseases.
          The object of the present invention is to provide
a method and a device for controlled, individualised medi-
cation in the treatment of complicated diseases whose
10 mechanisms are not fully known, thereby to improve the
patient's state of health.
          This object is attained by a method and a device hav-
ing the distinctive features recited in appended claims 1
and 9, respectively. Other features of the invention are
15 stated in the appended subclaims.
          The invention has the great advantage of automatical-
ly drawing conclusions from the inputted data as to what
activities, what external factors and what medication will
result in a satisfactory state of health for the patient.
20 On the basis of these conclusions, rules are established
regarding when and in what doses the different medicines
are to be taken. The thus-established rules are not fixed,
but are continuously refined upon with the aid of data
recorded by the patient. Thus, the invention gradually
25 "learns" what is needed for the well-being of the patient.
Further, the rules are automatically adapted to changes in
the patient without the device having to be reprogrammed.
          The invention will be described in more detail below
with reference to the accompanying drawing, which schema-
30 tically illustrates the structure of a device in accor-
dance with the invention.
          The aim of the invention is to give the patients con-
trolled, individualised and situation-dependent medication
advice, thereby to enhance the patient's sense of well-
35 being to an optimum extent. The inventive method is adap-
tive, i.e the basic rules for the advice are altered if
the relevant factors affecting the patient are changed.

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Conveniently, the invention is implemented in portable "wallet-size" computers.

As appears from the drawing, the method is founded on a knowledge-based computer system or expert system 6

5   having a reminder function 1, a recording and storage function 2, 3, as well as a function 4 for inductive rule generation.

When the system is operating, the reminder function 1 is normally activated. The computer emits a signal when

10 a pharmaceutical preparation is to be taken (or some other activity is to be performed), and advises on the type of preparation to be taken as well as the dosage. In the recording function 2 of the system, the patient confirms that the medicine has been taken, and then indicates his

15 current state of health by responding to questions put to him by the computer. In addition, the patient separately records other relevant events, such as awakening, intake of food, exercise and stress, when these occur, and also indicates his current state of health.

20   These data are stored in a database 3 together with the point of time at issue. Optionally, some information may be automatically retrieved by sensors.

The information, which constitutes a situation data-base 3, is used for determining relevant relations in time

25 between various events and to generate examples distin-guishing the different symptoms that are to be controlled. The examples consist of values for the attributes (affect-ing factors) that are relevant, as well as the associated symptom value (conclusion). The attributes used for each

30 preparation are, among others, "latest dosage", "time from intake", and "remaining duration of action".

Collections of examples are automatically created every day for each group of symptoms. These collections are accumulated in a "rolling" database, preferably

35 including the values from the last 20 days. The examples are then used in each group of symptoms for spotting, with the aid of prior-art inductive data analysis 4, the rela-

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tionships that exist, and drafting rules for predicting
the symptoms.

Inductive data analysis and rule generation are
described in, inter alia, the following publications:
5   Quinlan, JR (1979), Discovering Rules by Induction from
Large Collections of Examples, Introductory Readings in
Expert Systems (D. Michie), pp 33-46, London; Gordon and
Breach 1979. Quinlan, JR (1983), Learning from Noisy Data,
Proceedings of the International Machine Learning Work-
10 shop, University of Illinois, pp 58-64, 1986.

The prediction rules are generated in the form of
decision trees and/or so-called conditional rules of the
type:
IF $X1<0.12$ AND $Z3=$"protein B" AND $Z1>0.34$ AND $Z2=2$ THEN
15 RIGIDITY = "excessive agility".

The rules are validated by being tested at 5 against
borderline cases drawn up on long-term experience. Approv-
ed rules are transferred to the knowledge base in an
20 expert system 6 in known manner. The expert system may be
a conventional rule-based system or be based on fuzzy
logic. Then, the expert system is able to predict the
state of health of the patient by part predictions of the
various symptoms in a specific situation.
25   When in use, the expert system is automatically
called at 8 at regular time intervals, preferably every
fifth minute. When called, the system is consulted with
respect to the current values from the situation database.
In consultation, time data are displaced forwards, pre-
30 ferably by a time factor corresponding to the time elaps-
ing from the intake of a preparation to the attainment of
its biophase. This makes it possible for the system to
signal before any undesirable effects appear (early warn-
ing system). The consultation is performed in known manner
35 via "backward chaining", i.e. starting from a desirable

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conclusion (state of health). Desirable conclusions can be
predetermined for every group of symptoms.

The expert system operates in real time and can, in
each specific situation, find in good time the prerequi-
5   sites and conditions that have to be met to achieve the
desired state of health. If this state cannot be achieved
in a specific situation (e.g. because the patient has
forgotten to act on previous advice), the system looks for
the prerequisites for attaining the "second-best" state of
10   health. Induction of rules and updating of the knowledge
base are performed automatically by the system, conve-
niently once every twenty-fourth hour. Because the system
learns to detect patterns by induction of real situations,
the system can provide individualised medication advice
15   without having access to explicit causal connections and
pharmacological data, the prerequisite being that the
attributes used directly or indirectly represent patterns
that can be classified. According to the invention, the
patient records the point of time when he takes the
20   various preparations, the dosage as well as his current
state of health. These data are used for generating, by
inductive data analysis, prediction rules that are used
for providing advice on the point of time and the dosage.

For each preparation, one starts from a patient-spe-
25   cific longest nominal duration of action. In the examples,
the remaining duration of action as well as the dosage of
the latest and the latest-but-one intake are determined.
Also other relevant factors, such as the intake of food,
state of stress and related time, are also included in the
30   examples.

The prediction rules generated by prior-art inductive
data analysis are called at predetermined intervals, and
a time delay is then introduced, which preferably corre-
sponds to the time elapsing, in the case of the different
35   preparations, from the intake to the attainment of the
biophase. The prediction rules are called by backward
chain, primarily in order to satisfy the current situation

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to attain the desired state of health. If any of the con-
ditions that can be influenced is not satisfied, e.g. the
dosage of a preparation, the system will recommend that
this be done.

5   A mode of operation of the invention, intended for
controlled, individualised adaptive medication in the
treatment of Parkinson's disease, will be described below.
In Parkinson's disease, the body cannot produce sufficient
amounts of a neurotransmitter in the brain called dopa-

10   mine, which results in limitations of movement, muscular
cramp and tremor. This state can be counteracted by the
supply of various preparations, such as L-dopa, which are
converted to dopamine or the substance bromokriptin. In
order to master undesirable side-effects, such as effects

15   on the blood pressure, these preparations generally have
to be combined with other medicines. Thus, medication fre-
quently involves at least three different preparations,
each having a specific dosage and a specific time inter-
val between administrations. Owing to the interactions

20   taking place, the time intervals and the doses have to be
adapted to one another. Also external factors, such as the
intake of food, exercise and state of stress, affect the
action of the preparations. As a result, patients that
have been ill for a long time, and thus have had plenty of

25   time to find which medication suits them best, are seldom
perfectly untroubled for a whole day. Frequently, there
are two or more periods during the day in which they expe-
rience considerable discomfort in the form of tremor,
rigidity and "dullness of mind". Too low a dosage typi-

30   cally results in tremor, rigidity and muscular cramp. Dis-
comfort caused by overdosage is not less common, manifest-
ing itself in the form of uncontrolled excessive agility,
among other things. The reminder function indicates when
the preparations, such as Pravidel, Sinemet, Inderal,

35   Madopark, and Eldepryl, are to be taken, and further pro-
vides recommendations as to the intake of liquid, food and
rest.

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The recording function includes compulsory input of
the state of health expressed as degrees of the attributes
"Rigidity", "Agility", "Tremor" and "Dullness of Mind".
Recordation is also performed when other important events
5   take place, such as "awakening", "falling asleep", "eat-
ing" and "drinking". In recordation, the time is indicated
in minutes from the awakening.

When generating examples, the times elapsing from the
intake of the various preparations and events to the pre-
10 sent time are determined. Two times are preferably deter-
mined for each preparation, namely the time that has
elapsed from the latest-but-one intake and the time that
has elapsed from the latest intake.

A nominal duration of action from the intake is used
15 for the various preparations. When the individual duration
of action is known, this is indicated.

At the end of each day, a collection of examples
with attribute values determined as above is created.
The recorded state of health is indicated as conclusion
20 for each example.

A collection of examples is thus made for each of the
indicated states of health, i.e. one collection of exam-
ples with the conclusion related to "Rigidity", one col-
lection related to "Tremor", and one collection related to
25 "Dullness of Mind". Then, rules are induced from the col-
lections of examples, and the rules are validated by com-
paring their threshold values with indicated maximum and
minimum limits as to dosage and time.

If a rule falls outside these limits, the indicated
30 limit values are used.

Thereafter, the rules are transferred to the know-
ledge base in a deductive expert system.

The generation of examples, the induction and the
transfer to the database are initiated at the end of each
35 day and are perfectly automatic.

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When using the system, the reminder function is acti-
vated when the patient starts the computer upon awakening.

The reminder function calls the expert system at
intervals of preferably about 5 min, and the expert system
5   is thus consulted with respect to the data recorded. In
consultation, an advance time corresponding to the average
time elapsing from the intake of a preparation to its com-
menced action, is added to the real time. Preferably, the
advance time is 30 min. Consequently, the system will be
10   able to issue reminders in good time.

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CLAIMS

1. A method for controlled, individualised medica-
5   tion, c h a r a c t e r i s e d by
recording, every time the patient takes his medicine,
the type of medicine, the dose and the point of time in a
database,
recording information on the patient's state of health
10 on recurrent occasions in the database,
analysing the information recorded in the database by
means of inductive data analysis in order to establish
medication rules on the basis of detected relationships
between the patient's intake of medicine and his state of
15 health,
comparing the established medication rules with pre-
determined medication conditions for approval,
using the approved rules for continuously deciding
whether medication is to be performed and, if so, deciding
20 the type of medicine and the dose, and
repeating the analysis of the database for conti-
nuously optimising the medication rules with the aid of
new information recorded in the database and for adapting
the rules to changes in the patient's state of health.
25   2. A method as set forth in claim 1, c h a r a c -
t e r i s e d by the medication comprising the admini-
stration of at least two different medicines.
3. A method as set forth in claim 1 or 2, c h a r -
a c t e r i s e d by also recording information on the
30 patient's intake of food and his activities in the data-
base, and taking this information into consideration when
establishing the medication rules.
4. A method as set forth in any one of the preceding
claims, c h a r a c t e r i s e d by always recording
35 the patient's state of health when recording his intake of
medicine.

11

5. A method as set forth in any one of the preced-
ing claims, c h a r a c t e r i s e d by calculating
the relations in time between various external events
recorded and the state of health recorded.

5   6. A method as set forth in any one of the preced-
ing claims, c h a r a c t e r i s e d by allotting a
duration of action to each medicine, and continuously
calculating the remaining duration of action of the
medicine taken.

10   7. A method as set forth in any one of the preced-
ing claims, c h a r a c t e r i s e d by using the dose
and the remaining duration of action as attributes in the
inductive data analysis.

8. A method as set forth in any one of the preced-
15 ing claims, c h a r a c t e r i s e d by being used in
the treatment of Parkinson's disease.

9. A device for controlled, individualised medica-
tion, c h a r a c t e r i s e d by means (2) for record-
ing information on the intake of medicine and the pa-
20 tient's state of health, a database (3) for storing this
information, a program (4) for performing an inductive
analysis of the information stored in the database and
establishing medication rules on the basis of detected
relationships between the intake of medicine and the
25 patient's state of health, memory means (5) for storing
predetermined medication conditions, means (5) for com-
paring the medication rules established by means of the
program for performing inductive analysis and the pre-
determined medication conditions for approval of the medi-
30 cation rules, an expert system (6) where the approved
rules are used for deciding whether medication is to be
performed and, if so, which type of medicine and what dose
should be given, means (7) for activating the program for
inductive analysis at given points of time, and means (8)
35 for polling the expert system at given points of time.
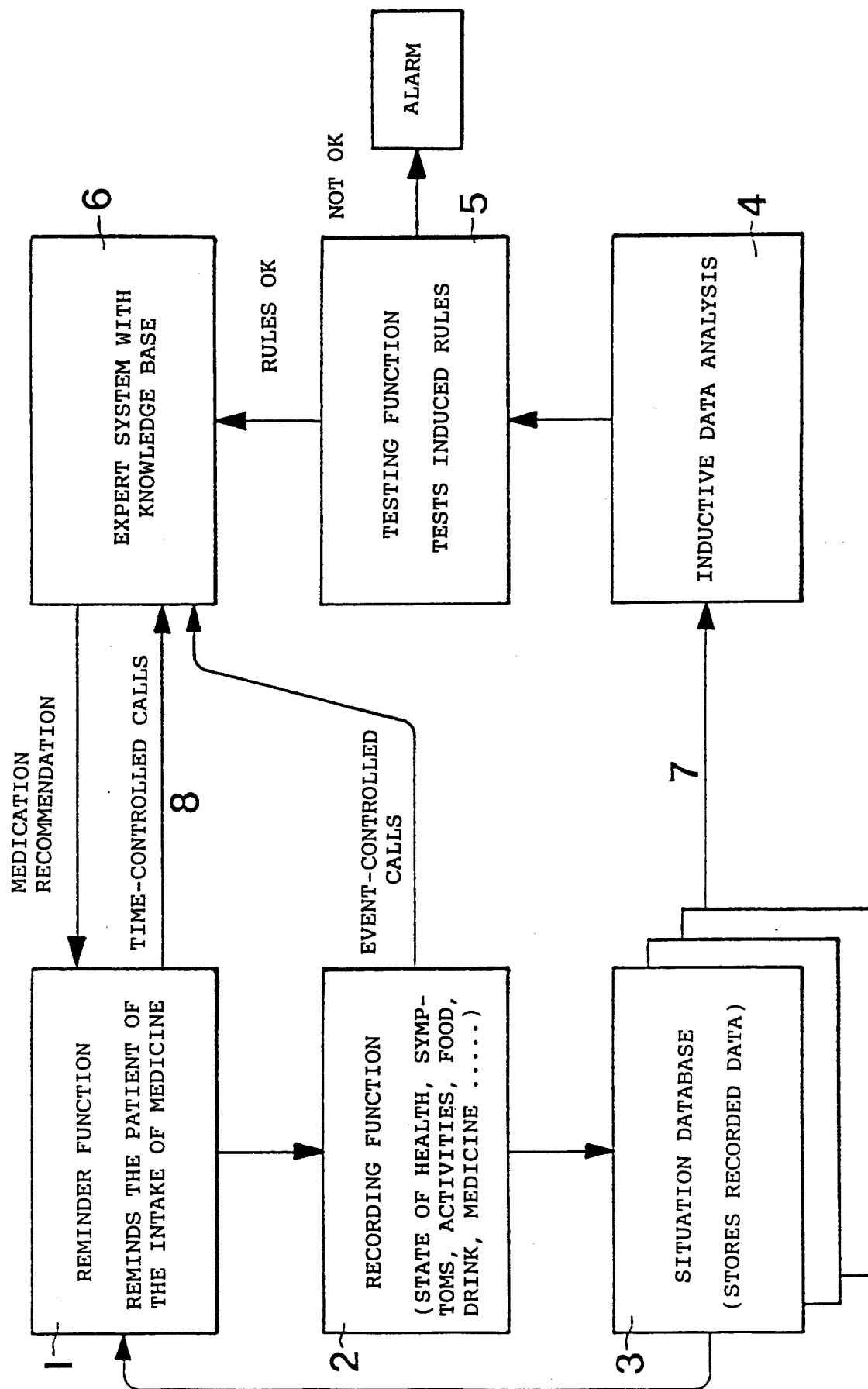
INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00708

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: G06F 15/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A2, 0303930 (SYNTHES AG), 22 February 1989 (22.02.89)	1-9
A	GB, A, 2218831 (MARK JOHN NEWLAND), 22 November 1989 (22.11.89)	1-9
A	US, A, 5019974 (ANDREAS G.F. BECKERS), 28 May 1991 (28.05.91)	1-9
A	EP, A1, 0128054 (SIMATEC S.A.R.L.), 12 December 1984 (12.12.84)	1-9

☐ Further documents are listed in the continuation of Box C.   ☒ See patent family annex.

*	Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1993	01 -12- 1993

Name and mailing address of the ISA/	Authorized officer
Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Jan Silfverling Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

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GB-A- 2218831	22/11/89	NONE	
US-A- 5019974	28/05/91	EP-A- 0290683	17/11/88
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